

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**

**THIS PAGE BLANK (USPTO)**

(12) UK Patent Application (19) GB (11) 2 254 556 (13) A  
(43) Date of A publication 14.10.1992

(21) Application No 9207832.8

(22) Date of filing 09.04.1992

(30) Priority data  
(31) 9107640 (32) 11.04.1991 (33) GB  
9107669

(71) Applicant  
Fisons plc  
(Incorporated in the United Kingdom)  
Fison House, Princes Street, Ipswich, IP1 1QH,  
United Kingdom

(72) Inventors  
Steven Hewitt  
Susan Mary Williams

(74) Agent and/or Address for Service  
S P Gilholm  
Fisons plc, 12 Derby Road, Loughborough,  
Leicestershire, LE11 0BB, United Kingdom

(51) INT CL<sup>5</sup>  
A61K 31/20 31/19 31/44 33/06 33/10 33/26

(52) UK CL (Edition K)  
A5B BJA B170 B180 B190 B26Y B27Y B271 B272  
B28Y B280 B285 B36Y B360 B361 B362 B363  
B364  
U1S S1317

(56) Documents cited  
GB 2134782 A EP 0261814 A2 EP 0246734 A1  
US 4855136 A US 4851431 A

(58) Field of search  
UK CL (Edition K) A5B BJA BJB BJC  
INT CL<sup>5</sup> A61K  
Online databases: WPI, CLAIMS, CAS ONLINE

(54) Linolenic acid formulations

(57) Pharmaceutical or dietary compositions comprise a linolenic acid and a calcium source, an iron source and/or vitamin B6 in admixture with a carrier.

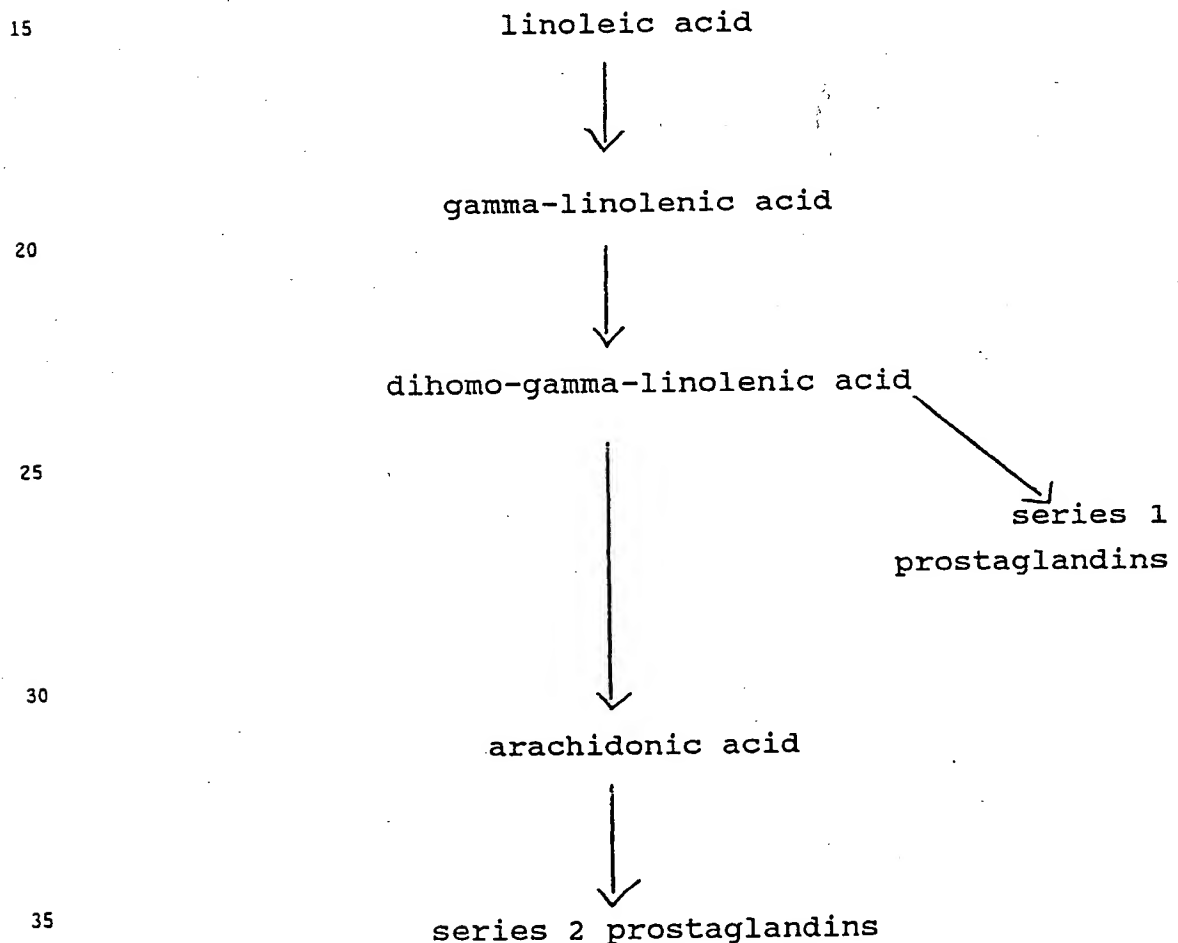
Compositions are for administration to adolescent girls to prevent the onset of premenstrual syndrome.

Other ingredients which may be included in the compositions are e.g. magnesium, vitamins A, B1, B2, B3, B12, folic acid, C, D and E. Calcium and iron sources can be calcium carbonate, gluconate or dicalcium phosphate, FeSO<sub>4</sub>, ferrous gluconate or fumarate. Linolenic acid may be in form of GLA and/or DGLA.

Formulations

This invention relates to new pharmaceutical formulations and their method of use. In particular it relates to formulations comprising a linolenic acid and certain minerals and optionally, vitamins which are useful in the treatment, alleviation of prophylaxis of certain disorders, and especially premenstrual syndrome.

There has been considerable interest in recent years in the manipulation of prostaglandin synthetic pathways. This can be achieved by manipulating the dietary intake (and hence tissue incorporation) of the fatty acids which form part of the prostaglandin synthetic pathway. The pathway for conversion is thought to be:



One condition in humans ie females which is amenable to treatment by influencing the prostaglandin synthetic pathways is premenstrual syndrome (PMS). The condition has been treated by administration of gamma-linolenic acid (GLA), given orally as Evening Primrose Oil.

By enhancing the endogenous production of series 1 prostaglandins such as PGE1, the symptoms of PMS can be controlled.

Brush et al (American Journal of Obstetrics and Gynaecology, Volume 150, pages 363-366, 1984) have also shown that essential fatty acid levels are abnormal in women suffering from PMS; in particular the circulating level of GLA is low. Brush has also described oral supplementation with a source of GLA as a successful treatment for PMS.

On reaching puberty, girls experience a number of problems which can be alleviated by nutritional means. Not only do they run the risk of suffering PMS (it is estimated that some 60% of Western women experience PMS) with its disruptive effect on education and social life, but onset of menstrual blood loss also places the adolescent girl at risk of anaemia through poor prepubertal iron status.

It is also at puberty when girls are especially susceptible to calcium deficiency which can, in later life, lead to osteoporosis, or brittle bone disease.

Many girls, at puberty, become more self-aware and often experience a desire to lose weight by dieting. Poor food choice and avoidance of nutrient-dense foods such as meat and dairy products place the adolescent girl at risk of general vitamin and mineral deficiency, but particularly, as discussed above, deficiency of calcium and iron.

Another approach in the alleviation of PMS is the administration of vitamin B6. This agent is thought to affect both the physical and mental disturbance caused by

PMS mainly through its influence on protein synthesis.

Gunn (International Journal of Vitamin Research Supplement 27, pages 213-224, 1985) has described the use of vitamin B6 in the treatment of PMS. Elsewhere Gunn also suggests that vitamin B6 deficiency may be an important factor in the onset of PMS.

The Committee on Dietary Allowances, Food and Nutrition Board (Recommended Daily Allowances, 9th Revised Edition, National Academy of Sciences, Washington DC, 1980) have set the Recommended Daily Amount (RDA) of vitamin B6 in girls aged 11 to 14 needed to maintain good health at 1.8 mg daily.

We have also found that the oral dose of vitamin B6 required to maintain body functions of this vitamin while replenishing the body stores is higher than the recommended RDA of 1.8 mg. In addition, we have found that combining high vitamin B6 levels with GLA supplementation is advantageous in the treatment or alleviation of PMS.

We have now surprisingly found that compositions containing GLA, and one or more of a calcium source, an iron source and vitamin B6 may be used to formulate a nutritional supplement primarily intended for administration to young adolescent girls which may act prophylactically and prevent the onset of PMS.

Thus according to the invention we provide a pharmaceutical or dietary composition comprising more than 0.09 mg of a linolenic acid or a physiologically functional derivative thereof and one or more of a calcium source, an iron source and vitamin B6 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

The calcium source may be, eg calcium carbonate, dicalcium phosphate or calcium gluconate. The amount of available calcium in the composition may be from 10mg to 5g, preferably from 10mg to 1g, more preferably from 10mg to 500mg, most preferably from 50mg to 500mg and especially

50mg to 250mg, eg 120mg.

The iron source may be, eg ferrous sulphate, ferrous gluconate or ferrous fumarate. The amount of available iron in the composition may be from 1 to 250mg, preferably from 1mg to 50mg, more preferably from 5mg to 50mg, most preferably from 5mg to 25mg and especially from 5mg to 15mg, eg 11mg.

We have discovered that certain daily doses of vitamin B6 or a physiologically functional derivative thereof will satisfy the daily requirement for this vitamin in adolescent girls whilst replenishing the body stores over a period of weeks. At such dose levels, the plasma level of the vitamin will not be elevated and so the likelihood of toxicity will be extremely low. Doses of less than 25 mg of vitamin B6 daily are reported to have no effect on plasma levels. The invention therefore offers a daily dose of more than 3.9mg of vitamin B6, preferably between 4mg and 1g, more preferably from 4mg to 25mg and most preferably 4mg to 15mg, eg from 4.4 to 15mg, and especially 10mg.

Any physiologically functional derivative of vitamin B6 may be used but specific derivatives which may be mentioned include pyridoxine, pyridoxal and pyridoxamine.

The linolenic acid of the formulation may be GLA or dihomogamma linolenic acid (DGLA) or a mixture of GLA and DGLA. The dose may of course vary depending on the age, size and weight of the adolescent girl which the formulation is intended to treat. The proposed formulations preferably offer between 0.1 mg and 1 g of GLA/DGLA as the daily dose; more preferably 1 mg to 500 mg, most preferably 5 mg to 50 mg and especially 5 mg to 25 mg, eg 10 mg. We especially prefer the source of linolenic acid to be GLA. Suitable sources of GLA include the seed oil of the evening primrose (*Oenothera* species), the blackcurrant, borage (*Borage* species) and oils produced by

5 fungal fermentation.

Magnesium is also a trace element in which pubescent girls are found to be deficient. Since vitamin B6 works on a protein complex containing magnesium we have found that  
5 by increasing the vitamin B6 levels in pubescent girls the level of magnesium supplementation may be reduced.

Thus according to the invention we provide a formulation as hereinbefore described containing from 10 to 200 mg of magnesium, preferably from 10 to 100 mg, more  
10 preferably 20 to 70 mg and most preferably 40 to 60 mg eg 50 mg of magnesium.

The invention may offer the above nutrients in combination with other vitamins and minerals in amounts between 5 percent and 500 percent of their recommended  
15 daily amount or allowance. Where no recommendations are made, inclusion of the vitamin or mineral will be based on known toxicity data for the nutrient and will be appropriate to the age of the intended recipient.

Other ingredients which may be included in the  
20 formulation are, in particular, vitamins A, B1, B2, B3, B12, C, D and E, and folic acid. These vitamins may be present at the recommended daily dose for a young adolescent girl.

The quantities of additional ingredients may vary, but  
25 we prefer one or more of the following ranges:

Vitamin A	from 100 to 2,200 $\mu$ g	400 $\mu$ g
Vitamin B1	from 0.1 $\mu$ g to 30 mg,	eg 0.6 mg
Vitamin B2	from 0.2 mg to 4.2 mg,	eg 0.9 mg
Vitamin B3	from 2.0 mg to 50 mg,	eg 10 mg
30 Vitamin B12	from 0.3 $\mu$ g to 10 $\mu$ g,	eg 1 $\mu$ g
Vitamin C	from 3.0 mg to 100 mg,	eg 22 mg
Vitamin D	from 0.3 $\mu$ g to 10 $\mu$ g,	eg 2.5 $\mu$ g
Vitamin E	from 1.0 mg to 25 mg,	eg 5 mg
Folic Acid	from 20 $\mu$ g to 600 $\mu$ g,	eg 150 $\mu$ g

35 The compositions according to the invention are



advantageous in that they are more efficaceous, than other known formulations. In particular, the compositions according to the present invention exhibit improvements such as increased energy, fewer symptoms of premenstrual  
5 tension and improved condition of skin and nails in pubescent females. The compositions according to this invention are conveniently in a form suitable for oral, rectal, topical or parenteral administration in a suitable pharmaceutical vehicle. Thus for example, capsules,  
10 tablets, ingestible liquids or foods may be used as required.

We prefer compositions which are designed to be taken oesophageally and to release their contents in the gastrointestinal tract. The compositions may be in the  
15 form of tablets which may, for example, be made by direct compression. In such a process the dietary supplements are mixed with a pharmaceutically acceptable adjuvant, diluent or carrier which may be one or more of modified forms of starch, calcium phosphate, a sugar eg lactose,  
20 microcrystalline cellulose and/or other directly compressible excipients, together with lubricant(s), eg stearic acid or magnesium stearate, flow aid(s), eg talc or colloidal silicon dioxide, and disintegrant(s), eg starch or the materials sold under the Trade Marks, Nymcel,  
25 Ac-Di-Sol, Explotab and Plasdone XL." Tablets are then formed by direct compression, and may be sugar or film coated eg with hydroxypropylmethylcellulose.

However, we prefer the dietary supplements to be dissolved in a suitable solvent, eg polyethylene glycol,  
30 Gelucaire, arachis oil, a (hydrogenated) vegetable oil or beeswax and the solution is then filled into a gelatin capsule.

It will be understood that the absolute quantity of active ingredients present in any dose unit should be  
35 sufficient to allow dosing in a convenient number of

doses. The rate of administration will depend upon the pharmaceutical action required.

The following examples serve to illustrate pharmaceutical compositions according to the invention.

5 Example 1

A gelatin capsule containing the following ingredients in an appropriately preserved excipient base:

	Gamma linolenic acid	9 mg
	as Evening Primrose Oil	
10	Vitamin B6	10 mg
	Vitamin A	400 µg
	as retinoids or carotenoids	
	Vitamin B1 (thiamin)	0.6 mg
	Vitamin B2 (riboflavin)	0.9 mg
15	Vitamin B3 (niacin)	10 mg
	Vitamin B12 (cyanocobalamin)	1 µg
	Folic Acid	150 µg
	Vitamin C	22 mg
	Vitamin D	2.5 µg
20	Vitamin E	5 mg
	Calcium	120 mg
	Iron	11.4 mg
	Magnesium	50 mg

This capsule formulation to be taken one daily as a  
25 food supplement for girls aged 9 years upwards.

Example 2

A gelatin capsule containing the following ingredients in an appropriate preserved excipient base:

	Gamma linolenic acid	18 mg
30	as borage oil	100 mg
	Vitamin B6	10 mg
	Vitamin B12	2 µg
	Folic Acid	200 µg
	Vitamin C	25 mg
35	Calcium	120 mg

Iron	12 mg
Magnesium	50 mg

This capsule presentation to be taken one daily for the relief and/or prevention of the symptoms of premenstrual syndrome in young girls and women.

Example 3

A gelatin capsule containing the following ingredients in an appropriately preserved excipient base:

	Gamma linolenic acid	9 mg
10	as Evening Primrose oil	100 mg
	Vitamin B6	20 mg
	Vitamin A	750 µg
	as retinoids or carotenoids	
	Vitamin B1 (thiamin)	1.2 mg
15	Vitamin B2 (riboflavin)	1.6 mg
	Vitamin B3 (niacin)	1.8 mg
	Vitamin B12 (cyanocobalamin)	2 µg
	Folic Acid	200 µg
	Vitamin C	30 mg
20	Vitamin D	2.5 µg
	Vitamin E	10 mg
	Calcium	120 mg
	Iron	12 mg

This capsule formulation to be taken one daily as a food supplement for girls aged 9 years upwards.

Example 4

A gelatin capsule containing the following ingredients in an appropriately preserved excipient base:

	Gamma linolenic acid	9 mg
30	as Evening Primrose Oil	
	Vitamin B6	10 mg
	Vitamin A	400 µg
	as retinoids or carotenoids	
	Vitamin B1 (thiamin)	0.6 mg
35	Vitamin B2 (riboflavin)	0.9 mg

	Vitamin B3 (niacin)	10 mg
	Vitamin B12 (cyanocobalamin)	1 µg
	Folic Acid	150 µg
	Vitamin C	22 mg
5	Vitamin D	2.5 µg
	Vitamin E	5 mg
	Calcium	120 mg
	Magnesium	50 mg

This capsule formulation to be taken one daily as a  
10 food supplement for girls aged 9 years upwards.

Example 5

A gelatin capsule containing the following ingredients  
in an appropriately preserved excipient base:

	Gamma linolenic acid	9 mg
15	as Evening Primrose Oil	
	Vitamin B6	10 mg
	Vitamin A	400 µg
	as retinoids or carotenoids	
	Vitamin B1 (thiamin)	0.6 mg
20	Vitamin B2 (riboflavin)	0.9 mg
	Vitamin B3 (niacin)	10 mg
	Vitamin B12 (cyanocobalamin)	1 µg
	Folic Acid	150 µg
	Vitamin C	22 mg
25	Vitamin D	2.5 µg
	Vitamin E	5 mg
	Iron	11.4 mg
	Magnesium	50 mg

This capsule formulation to be taken one daily as a  
30 food supplement for girls aged 9 years upwards.

Example 6

A sample of pubescent females were given daily doses  
of the formulation according to Example 1 for a period of  
two months.

35 Their improvements in:-

- (i) increased energy
  - (ii) fewer symptoms of premenstrual tension
  - (iii) condition of skin and nails
- were noted.

5

10

15

20

25

30

We Claim

1. A pharmaceutical or dietary composition comprising more than 0.09 mg of a linolenic acid or a physiologically functional derivative thereof and one or more of a calcium source, and iron source and vitamin B6 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
2. A composition according to Claim 1 comprising from 10mg to 5g of a calcium source.
3. A composition according to Claim 1 comprising from 1 to 250mg of available iron.
4. A composition according to Claim 1 comprising from more than 3.9mg of vitamin B6
5. A pharmaceutical or dietary composition according to Claim 2 comprising 120 mg of a calcium source.
6. A pharmaceutical or dietary composition according to Claim 3 containing 11 mg of available iron.
7. A pharmaceutical or dietary composition according to Claim 3 wherein the source of the iron is ferrous sulphate.
8. A pharmaceutical or dietary composition according to Claim 3 wherein the source of the iron is ferrous gluconate.
9. A pharmaceutical or dietary composition according to Claim 3 wherein the source of the iron is ferrous fumarate.
10. A pharmaceutical or dietary composition according to Claim 4 comprising from 4 mg to 1 g of vitamin B6.
11. A pharmaceutical or dietary composition according to Claim 4 comprising 10 mg of vitamin B6.
12. A pharmaceutical or dietary composition according to Claim 4 wherein the vitamin B6 derivative is pyridoxine.
13. A pharmaceutical or dietary composition according to Claim 4 wherein the vitamin B6 derivative is pyridoxal.
14. A pharmaceutical or dietary composition according to Claim 4 wherein the vitamin B6 derivative is pyridoxamine.
15. A pharmaceutical or dietary composition according to Claim 1 comprising from 0.1 mg to 1g of a linolenic acid.

16. A pharmaceutical or dietary composition according to Claim 15 comprising 10 mg of a linolenic acid.
17. A pharmaceutical or dietary composition according to Claim 1 wherein the linolenic acid or a physiologically functional derivative thereof is dihomogamma linolenic acid (DGLA).
18. A pharmaceutical or dietary composition according to Claim 1 wherein the linolenic acid or a physiologically functional derivative thereof is gamma linolenic acid (GLA).
19. A pharmaceutical or dietary composition according to Claim 1 wherein the linolenic acid or a physiologically functional derivative thereof is a mixture of GLA and DGLA.
20. A pharmaceutical or dietary composition according to Claim 1 wherein the source of the GLA is the seed oil of the evening primrose (*Oenothera* species).
21. A pharmaceutical or dietary composition according to Claim 1 wherein the source of the GLA is the blackcurrant.
22. A pharmaceutical or dietary composition according to Claim 1 wherein the source of the GLA is borage (*Borage* species).
23. A pharmaceutical or dietary composition according to Claim 1 wherein the source of the GLA is an oil or oils produced by fungal fermentation.
24. A pharmaceutical or dietary composition according to any one of the preceding Claims comprising from 10 to 200 mg of magnesium.
25. A pharmaceutical or dietary composition according to Claim 24 comprising 50 mg of magnesium.
26. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 100 to 2,200  $\mu\text{g}$  of Vitamin A.
27. A pharmaceutical or dietary composition according to Claim 26 containing 400  $\mu\text{g}$  of Vitamin A.
28. A pharmaceutical or dietary composition according to

- any one of the preceding Claims containing from 0.1  $\mu$ g to 30 mg of Vitamin B1.
29. A pharmaceutical or dietary composition according to Claim 28 containing 0.6 mg of Vitamin B1.
- 5 30. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 0.2 mg to 4.2 mg of Vitamin B2.
31. A pharmaceutical or dietary composition according to Claim 30 containing 0.9 mg of Vitamin B2.
- 10 32. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 2.0 mg to 50 mg of Vitamin B3.
33. A pharmaceutical or dietary composition according to Claim 32 containing 10 mg of Vitamin B3.
- 15 34. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 0.3  $\mu$ g to 10  $\mu$ g of Vitamin B12.
35. A pharmaceutical or dietary composition according to Claim 34 containing 1  $\mu$ g of Vitamin B12.
- 20 36. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 3.0 mg to 100 mg of Vitamin C.
37. A pharmaceutical or dietary composition according to Claim 36 containing 22 mg of Vitamin C.
- 25 38. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 0.3  $\mu$ g to 10  $\mu$ g of Vitamin D.
39. A pharmaceutical or dietary composition according to Claim 38 containing 2.5  $\mu$ g of Vitamin D.
- 30 40. A pharmaceutical or dietary composition according to any one of the preceding Claims containing from 1.0 mg to 25 mg of Vitamin E.
41. A pharmaceutical or dietary composition according to Claim 41 containing 5 mg of Vitamin E.
- 35 42. A pharmaceutical or dietary composition according to



- any one of the preceding Claims containing from 20  $\mu$ g to 600  $\mu$ g of folic acid.
43. A pharmaceutical or dietary composition according to Claim 42 containing 150  $\mu$ g of folic acid.
- 5 44. A pharmaceutical or dietary composition containing
- |                                |             |
|--------------------------------|-------------|
| Gamma linolenic acid           | 9 mg        |
| as Evening Primrose Oil        | 112.5 mg    |
| Vitamin B6                     | 10 mg       |
| Vitamin A                      | 400 $\mu$ g |
| 10 as retinoids or carotenoids |             |
| Vitamin B1 (thiamin)           | 0.6 $\mu$ g |
| Vitamin B2 (riboflavin)        | 0.9 mg      |
| Vitamin B3 (niacin)            | 10 mg       |
| Vitamin B12 (cyanocobalamin)   | 1 $\mu$ g   |
| 15 Folic Acid                  | 150 $\mu$ g |
| Vitamin C                      | 22 mg       |
| Vitamin D                      | 2.5 $\mu$ g |
| Vitamin E                      | 5 mg        |
| Calcium                        | 120 mg      |
| 20 Iron                        | 11.4 mg     |
| Magnesium                      | 50 mg       |
45. A pharmaceutical or dietary composition containing
- |                      |             |
|----------------------|-------------|
| Gamma linolenic acid | 18 mg       |
| as borage oil        | 100 mg      |
| 25 Vitamin B6        | 10 mg       |
| Vitamin B12          | 1 $\mu$ g   |
| Folic Acid           | 150 $\mu$ g |
| Vitamin C            | 22 mg       |
| Calcium              | 120 mg      |
| 30 Iron              | 11.4 mg     |
| Magnesium            | 50 mg       |
46. A pharmaceutical or dietary composition containing
- |                         |        |
|-------------------------|--------|
| Gamma linolenic acid    | 9 mg   |
| as Evening Primrose oil | 100 mg |
| 35 Vitamin B6           | 20 mg  |

	Vitamin A	750 µg
	as retinoids or carotenoids	
	Vitamin B1 (thiamin)	1.2 mg
	Vitamin B2 (riboflavin)	1.6 mg
5	Vitamin B3 (niacin)	1.8 mg
	Vitamin B12 (cyanocobalamin)	2 µg
	Folic Acid	200 µg
	Vitamin C	30 mg
	Vitamin D	2.5 µg
10	Vitamin E	10 mg
	Calcium	120 mg
	Iron	12 mg

47. A pharmaceutical or dietary composition as hereinbefore described.

15

20

25

30

Patents Act 1977  
Examiner's report to the Comptroller under  
Section 17 (The Search Report)

-16-

Application number

9207832.8

Relevant Technical fields

(i) UK CI (Edition K ) A5B (BJA, BJB, BJC)

(ii) Int Cl (Edition 5 ) A61K

Search Examiner

M R WENDT

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: WPI, CLAIMS, CAS ONLINE

Date of Search

16 JUNE 1992

Documents considered relevant following a search in respect of claims

1-47

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	GB A 2134782 (SENTRACHEM) See Claims 1-2, 7-13 Page 3 lines 37-41	1,18,24, 26,37,41
X	EP A2 0261814 (EFAMOL) See claims and examples	1,2,18, 20,22
X	EP A1 0246734 (EFAMOL) See Claim 1 and examples	1,3, 17-20,22 40
X	US A 4855136 (HORROBIN) See Claims 1, 2	1,2,5,15 18,20,22
X	US A 4851431 (BARK ILAN) See Claims 12, 18	1,12,24, 26,36,38 41,42

Category	Identity of document and relevant passages	Relevant to claim(s)

#### Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

**Databases:** The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).